

### **Remarks**

Claims 1-3, 7, and 16-21 were pending prior to this Response. By the present communication, no claims have been canceled, new claims 22 and 23 have been added, and claims 1, 16, and 20 have been amended to define Applicants' invention with greater particularity. Support for the amended claims may be found throughout the specification and claims as filed. Accordingly, upon entry of the present amendment, claims 1-3, 7, and 16-23 will be pending in this application.

### **Objection to the Claims**

Applicants respectfully traverse the objection to claims 1-3, 7, and 17-21 as allegedly containing informalities. Specifically, the Office Action alleges that claims 1 and 17 require purification of a Markush group of natural toxins. However, according to the Office Action, not all members of the Markush group is a natural toxin. Without acquiescing to the reasoning offered by the Office, and in order to expedite prosecution of the instant application, Applicants have amended step (a) of claim 1 to recite two separate Markush groups of toxins that may be purified. Since the mutant toxins are now grouped in a separate Markush group, Applicants submits that the Markush groups are proper. With regard to claim 17, Applicants respectfully submit that all toxins within the Markush group are natural toxins. More specifically, the recitation of "...or a mutant toxin thereof..." falls outside of the Markush group, as evidenced by the term "and" prior to "thermostable hemolytic toxin of *Vibrio parahaemolyticus*." However, in order to further separate the mutant toxins from those set forth in the Markush group, Applicants have amended claim 17 to insert a comma prior to "...or a mutant toxin thereof..." Withdrawal of this aspect of the object is respectfully requested.

The Office Action further points out that claim 20 contains a typographical error. Without acquiescing to the reasoning offered by the Office, and in order to expedite prosecution of the instant application, Applicants have amended claim 20 as suggested by the Examiner. Withdrawal of this aspect of the object is respectfully requested.

**Rejection under 35 U.S.C. § 103**

Applicants respectfully traverse the rejection of claims 1-3, 7, 16-18, 20, and 21 under 35 U.S.C. §103(a) as allegedly unpatentable over Giuliani, *et al.* J. Exp. Med. April 1998, Vol. 187, No. 7, 1123-1132 (hereinafter "Giuliani") in view of Esposito, *et al.* Infection and Immunity, July 1970, Vol. 2, No. 1, 120-22 (hereinafter, "Esposito"). The U.S. Supreme Court decision in the *KSR International v. Teleflex Inc.* (82 USPQ2d 1385), modified the standard for establishing a *prima facie* case of obviousness. Under the *KSR* rule, three basic criteria are considered. First, some suggestion or motivation to modify a reference or to combine the teachings of multiple references still has to be shown. Second, the combination has to suggest a reasonable expectation of success. Third, the prior art reference or combination has to teach or suggest all of the recited claim limitations. Factors such as the general state of the art and common sense may be considered when determining the feasibility of modifying and/or combining references.

The Office Action alleges that Giuliani teaches that LTR72, while having greatly reduced toxicity, still has a low residual level of toxicity. The Office Action relies upon Esposito for teaching a composition comprising attenuated cholera toxin, which is made by detoxification using formalin at a temperature of 35°. As such, the Office Action concludes that one of skill in the art would have been motivated to further attenuate LTR72 with formalin at a temperature of 35°, as set forth in Esposito.

Applicants respectfully disagree with the Examiner's position because there has been no motivation for one ordinary skilled in the art to combine teachings of Giuliani and Esposito. As indicated in the Office Action, Giuliani discloses that LTR72 still has a low residual level of toxicity. In fact, Giuliani states,

...it is likely that LTR72,...can be used safely in humans at high doses....[I]t is likely that LTR72 has the appropriate safety window to be safely used in the open population, including adults and children. (Giuliani, page 1129, left column, lines 7-13).

We have shown that although ADP-ribosylation activity is not necessary for the adjuvanticity of LT, the presence of low levels of enzymatic activity may be useful to induce faster and higher immune response to coadministered antigens.

This makes LTR72 an ideal adjuvant since without incurring problems of toxicity, it can take advantage of the adjuvant effect of low levels of enzymatic activity and of high doses of nontoxic AB complex. (Giuliani, page 1130, right column, Conclusions).

Applicants respectfully submit that from these cited passages, one of skill in the art would have understood that the residual toxicity (ADP-ribosylation activity) of LTR72 has no safety-related issues and is required to elicit an effective immune response. As such, for this reason alone, one of skill in the art would not have been motivated to further detoxify LTR72.

However, Applicants note that Giuliani further discloses that LTK63 is completely non-toxic (Giuliani, page 1126, left column, lines 1-2) and its adjuvanticity is inferior to that of wild-type LT and LTR72 (Giuliani, Figures 2-6). The results shown in Giuliani well conform to the art-recognized knowledge that a high level of detoxification reduces adjuvanticity, as described in the instant specification and repeatedly submitted in previous responses to Office Actions during prosecution of the instant application. As such, Applicants respectfully submit that one of skill in the art would have expected that further detoxification of LTR72 would reduce its adjuvanticity and therefore would not have been motivated to further detoxify LTR72, which Giuliani indicates has a good balance of safety and an effective immune response. Even if one of skill in the art would have thought to further detoxify LTR72, Applicants submit that there would have been no reasonable expectation of success in maintaining its adjuvanticity.

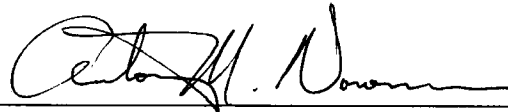
For the reasons set forth above, Applicants respectfully submit that one of skill in the art would not have contemplated further detoxification of LTR72 and would therefore have had no motivation to choose the formalin treatment taught by Esposito to combine with the disclosure of Giuliani. Thus, since Applicants identified the unexpected result of producing a highly attenuated toxins while retaining adjuvant activity, Applicants submit that a *prima facie* case of obviousness has not been established. Withdrawal of the rejection is respectfully requested.

**Conclusion**

In summary, for the reasons set forth herein, Applicants maintain that the claims clearly and patentably define the invention and respectfully request that the Examiner withdraw all rejections and pass the application to allowance. If the Examiner would like to discuss any of the issues raised in the Office Action, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

No fee is deemed necessary in connection with the filing of this paper. However, the Commissioner is hereby authorized to charge any fees that are required, or credit any overpayments to Deposit Account No. 07-1896 referencing the above-identified attorney docket number.

Respectfully submitted,



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